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On August 28, 2002

TOWNSEND and TOWNSEND and CREW LLP

By: _____

AMENDMENT UNDER 37 CFR 1.116
EXPEDITED PROCEDURE –
EXAMINING GROUP 1617

PATENT
Attorney Docket No.: 015662-000900US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

OG
9/23/02

In re application of:	Examiner: Nguyen, H.
MICHELINE MARKEY et al.	Art Unit: 1617
Application No.: 09/432,881	
Filed: November 2, 1999	
For: PHARMACOLOGICAL INDUCEMENT OF THE FED MODE FOR ENHANCED DRUG ADMINISTRATION TO THE STOMACH	

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1617

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Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This paper is submitted in response to the Final Office Action mailed May 23, 2002. Reconsideration of the application is respectfully requested in view of the following.

The withdrawal of the rejection of claim 2 under 35 U.S.C. 112 is acknowledged with appreciation, and the rejection under 35 U.S.C. 103 as obvious over Shell, Acharya et al., and Sewester et al. is once again traversed. The following explanation demonstrates how Applicants' invention as presently claimed is patentably distinct over these references, considered either alone or in combination.

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Applicants acknowledge that the claims under examination in this application are composition claims rather than method claims. The composition as recited in the instant claims is indeed distinct from those of the references, and from any composition that might be suggested by the references in combination. The limitations of Applicants' claims that are not met by the references are the recitation in claim 1 that the fed mode inducing agent is combined with a solid matrix that releases a drug when the matrix is in the stomach and that is large enough when in the stomach to promote gastric retention during the fed mode.

The dosage form that is disclosed by Acharya et al. is specifically formulated and configured for drug delivery in the mouth not in the stomach. The component in the Acharya et al. dosage form that controls the situs and manner of drug release is calcium polycarbophil, which is a bioadhesive typically used in vaginal products because of its tendency to adhere to the vaginal wall. In fact, polycarbophil adheres to mucus membranes in general. To corroborate this, Applicants submit the accompanying materials, downloaded from the internet, that discuss polycarbophil and how it functions in the products currently on the market in which it is used. The examiner is requested to make these materials of record. The pertinent disclosures in these materials are as follows:

I don't recall this request?

> The literature on *Replens* Vaginal Moisturizer downloaded from Yahoo Shopping website explains that polycarbophil "adheres to the epithelial cells lining the vaginal walls and … is detached only upon the shedding of the outer layer of cells or mucin, a normal healthy process which occurs every 2 or 3 days."
>
> The literature on Progesterone bioadhesive vaginal gel downloaded from Columbia Laboratories' website states that "Polycarbophil was designed to mimic negatively charged mucin, the glycoprotein component of mucous [*sic*, mucus] which is responsible for the attachment of mucus to underlying epithelial surfaces."

Carbophil performs the same function in the dosage form disclosed by Acharya et al. except that the mucus membrane in Acharya et al. is the inside of the

mouth rather than vaginal tissue. The dosage form is placed in the mouth for oral, gingival, or buccal delivery of the drug, this localized delivery being the result of the adherence of the polycarbophil to the oral, gingival, or buccal areas for an extended period of time (see column 3, lines 38-42). Further confirmation by Acharya et al. that the dosage form is one that remains in the mouth are found at column 7, lines 14-17, in the statement: "Most preferably, the shape of the polycarbophil follows the natural contour of the mouth ...," and at lines 31-33, in the statement: "While so present the hydrated polycarbophil acts to humidify the mouth, while in some instances also stimulating saliva production." All of these effects are achieved as a result of the retention of the dosage form in the mouth. Thus, the drugs that are disclosed in Acharya et al. are not "retained in a solid matrix in a manner causing release of said drug from said solid matrix when said solid matrix is in the stomach ..." Instead, they are retained in a solid matrix in a manner causing release of the drugs in the mouth, not the stomach. This is a difference in the matrix itself, specifically its composition, not in the manner in which the matrix is used. There is no suggestion that any of the drugs listed by Acharya et al. would serve any purpose in a matrix that releases the drug in the stomach rather than in the mouth.

Combining the Acharya et al. disclosure with that of Shell amounts to considering a dosage form that is specifically designed to remain in the stomach with one specifically designed to remain in the mouth. It is neither logical nor likely that one skilled in the art would take ingredients from one and transfer them to the other with the expectation that their usefulness or the function served by their presence in the mouth would be the same in the stomach. Accordingly, the combination of Shell and Acharya et al. does not lead one skilled in the art to include docusate, or any of the drugs disclosed by Acharya et al. in a gastric-retentive dosage form such as that disclosed by Shell.

As previously noted, the Sewester et al. disclosure describes docusate as a fecal softener, a function that is served in the colon. As in the case of Acharya et al., Sewester et al. do not suggest the inclusion of a fecal softener in a dosage form that remains in the stomach. Combining Sewester et al. with the other two references

amounts to considering a fecal softener that is specifically designed to act in the colon in combination with a dosage form that is specifically designed to deliver drugs to the stomach (Shell) where the fecal softener will not serve its known function, and also with a dosage form that is specifically designed to act in the mouth (Acharya et al.). The only common ground among these references is that the active ingredients are biologically active species. Aside from that, the disclosures are in direct contradiction to each other since each is focused on a distinct and different portion of the gastrointestinal tract and the results achieved are specifically intended to be occur only in those portions of the tract. There is no suggestion or motivation in any of the references to take a biologically active ingredient from a dosage form that restricts delivery of the active to the mouth and place it in a dosage form that restricts delivery to the stomach, or to take a biologically active ingredient that is known for its action in the colon and place it in a dosage form that restricts delivery to the stomach.

For these reasons, the combination of these references does not render obvious the invention recited in Applicants' claims, and the invention as claimed meets all requirements of the patent statute and is worthy of allowance. Accordingly, reconsideration is respectfully requested.

Applicants wish to point out that the election by Applicants in Paper No. 7 of docusate as a single disclosed species was a provisional election in accordance with MPEP 803.02 for the examiner to use as a starting point for a search. Since for the reasons explained above the generic claim to the extent of its coverage of docusate is allowable over the prior art, the search and examination should now be extended to include the remaining non-elected species.

> "On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." MPEP 803.02, p. 800-5, bottom of left column.

Should any matters remain that can be resolved by a conference, the examiner is encouraged to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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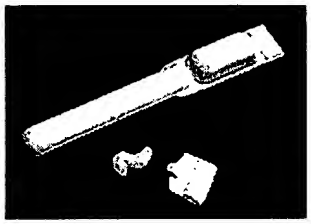
SF 1380090 v1

Healthcare Professional

Progesterone bioadhesive vaginal gel: scientific description

The bioadhesive vaginal gel contains micronized progesterone in an emulsion system, which is contained in single use, one piece, disposable white polyethylene vaginal applicator with a twist-off top. The carrier vehicle is an oil in water emulsion containing the water swellable, but insoluble polymer, polycarbophil. The progesterone is partially soluble in both the oil and water phase of the vehicle, with the majority of the progesterone existing as a suspension.



Each applicator contains 2.6 grams of bioadhesive gel and delivers 1.125 grams containing 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide and purified water. Physically, the gel has the appearance of a soft, white to off white gel.

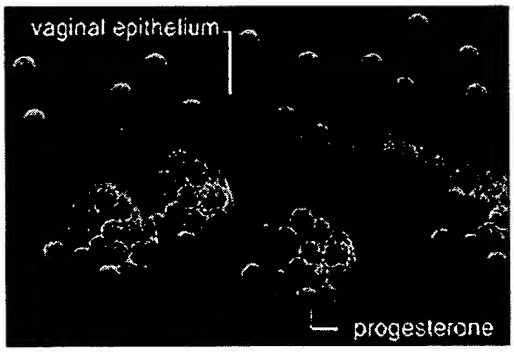
The active ingredient, progesterone, is present in an 8% concentration (w/w). The chemical name for progesterone is pregn-4-ene-3,20-dione and it is identical to the physiologic hormone.

Bioadhesion with polycarbophil: A new approach to progesterone delivery

The bioadhesive vaginal technology has been designed as a sustained-release system ensuring a constant and controlled release of progesterone for at least 48 hours after a single vaginal application. The constant and controlled release system of progesterone permits targeted progesterone delivery to the uterus thereby maximizing the desired effects in the uterus (preparation of the endometrium for implantation of an embryo and pregnancy support) while minimizing potential adverse effects because of low plasma progesterone concentrations. The constant and controlled release system is made possible by the polycarbophil which confers bioadhesive properties to the gel: polycarbophil adheres in the vagina for 72 hours or more.

P lycarbophil was designed to mimic negatively charged mucin, the glycoprotein component of mucous which is responsible for the attachment of mucus to underlying epithelial surfaces. Polycarbophil is a lightly cross-linked polymer. The cross linking agent is divinyl glycol. Polycarbophil is also a weak poly-acid containing multiple carboxyl radicals which is the source of its negative charges. These acid radicals permit hydrogen bonding with the cell surface. Hydrogen bonds are weak, but in the case of polycarbophil they are numerous and therefore, tenacious.[1,2] Polycarbophil is a water insoluble polymer and stays attached to the vaginal epithelial cells until they turn-over, normally up to 3 to 5 days.[3] If water soluble bioadhesive polymers were used, they would dissolve and be washed off the vaginal tissue within hours.

Since polycarbophil is a weak acid with a high buffering capacity it maintains the vaginal pH in the physiologic range, about 4.5 and thus, helps protect against infection.[3] In addition, polycarbophil shares with mucin the ability to adsorb 40 to 60 times its weight in water.[1,2] Polycarbophil is a very large molecule and therefore is not absorbed. It is also non-immunogenic, even in the laboratory it has not been possible to grow antibodies to the polymer. These characteristics make polycarbophil the ideal vehicle for vaginal administration of drugs.

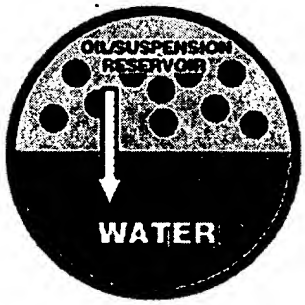


Polycarbophil containing vaginal products have been used by several hundred thousand women worldwide since 1989 without a single report of a serious adverse event related to the polymer.[4] Polycarbophil has vaginal moisturizing properties, by increasing the vaginal blood flow. Replens®, polycarbophil based moisturizing vaginal gel was developed by Columbia Laboratories and is used

to relieve the discomfort associated with vaginal dryness, particularly in menopausal women and women undergoing chemotherapy.

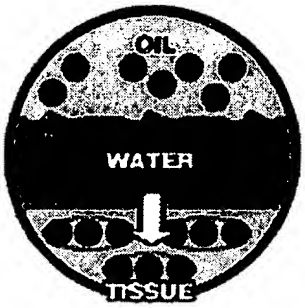
Contr lled and sustained releas of pr gesterone

The carrier vehicle for the controlled release formulation is an oil in water emulsion containing the polycarbophil. The progesterone is partially soluble in both the oil and water phase of the vehicle, with the majority of progesterone existing as a suspension.



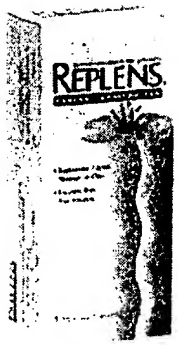
Progesterone is stored in the lipophilic fraction and is suspended in the gel thereby creating a reservoir for prolonged release. As small quantity of progesterone is also dissolved in the aqueous phase. From vaginal application as well as all other routes of administration only the drug in the aqueous fraction is available for diffusion into the uterus or absorption into the bloodstream. Hence, progesterone absorption from the gel is not dependent upon the presence of adequate local hydration because the progesterone dissolved in the aqueous phase is immediately available. Specifically, progesterone absorption from the gel is not dependent on the highly variable degree of vaginal secretions as is the case for oil based progesterone products and other non-hydrated formulations.

The oil and aqueous phase are in dynamic equilibrium: as progesterone diffuses from the aqueous phase into tissue or blood it is replaced by the progesterone stored in the oil phase or suspension reservoir. Thus, ensuring a controlled release of progesterone. The polycarbophil based bioadhesive delivery system also assures a sustained release of progesterone.



References:

1. Robinson JR, Leung SHS. Mechanisms of adhesion of swelling insoluble polymers to mucin epithelial surfaces. Proceedings of the 12th International Symposium on Controlled Release of Bioactive Materials;1985:12.
2. Park H., Robinson JR. Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion. J Control Release 1985;2:47-57, Elsevier Science Publishers B.V, Amsterdam.
3. March C, Nakamura R. Evaluation of the duration of effect of a bioadhesive vaginal moisturizing gel on vaginal pH. 7th International Congress on the Menopause, Replens® Symposium 1993;Stockholm, Sweden, June 20-22.
4. Data on file. Columbia Research Laboratories.



Replenishes Vaginal Moisture for Days.
Estrogen-Free, Non-Irritating.
Lowest Prices on the Web!

Each easy-to use, disposable applicator provides long-lasting comfort which lasts days. Non-Staining, non-irritating, and fragrance-free. Replens is the #1 recomm choice by gynecologists for relieving vaginal dryness. Contains no estrogen.

• Replens is moisture

For many women, vaginal dryness is a very real problem, which impacts their qu life. Fortunately, there is a safe and proven solution for vaginal dryness. It's calle Replens. A long-lasting, estrogen-free vaginal moisturizer, Replens helps women good about themselves again. Replens is the vaginal moisturizer recommend most by gynecologists. It replenishe moisture on a sustained basis for days, and relieves discomfort associated with vaginal dryness. Vaginal dryness more than 20 million women in the United States alone. long-lasting vaginal moisturizer Exclusive, patented bioadl delivery system adheres to vaginal epithelium for days. • Buffers vaginal pH to physiologic range compatible with a vaginal environment. • The only vaginal moisturizer to guarantee benefits that can last for days. • Minimizes leakag staining. • Non-irritating and fragrance-free. • Special soothing, natural-feeling lubrication formula, with a pH of 3.0 like normal vaginal environment. • Non-immunogenic, hypoallergenic, estrogen-free. • Prefilled single-use applicat made of soft, pliable polymer designed for comfort and ease of use.

• Complete, long lasting solution

Unlike vaginal lubricants, Replens is a vaginal moisturizer, acting directly on the tissue to make it less dry. Replens added advantage of being pH balanced, a fact that helps to keep the vagina acidic and less inviting for infection. R patented formula is guaranteed to restore vaginal moisture for up to 72 hours. Replens is the preferred choice for t of vaginal dryness by gynecologist worldwide.

The problem of vaginal dryness extends far beyond a mere comfort issue. If left untreated, the vaginal walls becon irritated, leading to bleeding, vaginitis, painful urination, bladder infection and painful intercourse. Vaginal dryness medical concern, one that demands a long-lasting, clinically proven solution.

• Knowledge is power

A national survey conducted by the makers of gynecologist- recommended Replens vaginal moisturizer reveals th women aren't knowledgeable about the difference between vaginal moisturizers and lubricants. Unlike standard lu like K-Y Jelly and Astroglide, Replens uses its patented bioadhesive delivery system to restore vaginal moisture fo 72 hours per application. Clinical studies have proven that with regular use, Replens can reverse the effects of vag dryness.

• Clinically proven and effective

Helps sustain vaginal moisture with a comfortable coating. • Helps maintain vaginal epithelial integrity, vaginal elas Compatible with condoms – does not alter their effectiveness.1 • Does not alter sperm motility or ovum penetration some lubricants. • Offers greater convenience and spontaneity for sexual intimacy in addition to providing overall v comfort for an extended time period.

References: 1Sato R, Sugiuchi A, Nakamura RM. A nonhormonal bioadhesive vaginal moisturizer. Clin Pract Sexu 1998;(5):1-5. 2Trishman GN, Luciano AA, Maier OB. Evaluation of Astroglide, a new vaginal lubricant; effects of le exposure and concentration on sperm motility. Fertil Steril. 1992;58:630 632.

ACTION AND CLINICAL PHARMACOLOGY: Polycarbophil, the key ingredient, is a bioadhesive polymer which ca up to 60 times its weight in water. It adheres to the epithelial cells lining the vaginal walls and delivers electrolytes

water. The polymer is detached only upon the shedding of the outer layer of cells or mucin, a normal healthy proce which occurs every 2 or 3 days. The polycarbophil is negatively charged and this causes the water and electrolyte: driven into the underlying cells. Electrolytes are also driven into the vasculature causing vasodilation, which results increase in blood supply to the tissue and (ii) a greater transudation of fluids which pass into and through the tissu electrolytes and water moisturize and lubricate the vaginal tissue and thus relieve the discomfort caused by vagina dryness. The increased blood flow can lead to enhanced secretion as vaginal fluids diffuse from blood.

In addition, the polymer, polycarbophil, has a low pH of 2.8 and has the ability to keep the pH of the vagina stable. maintains vaginal pH in the physiologically normal range (4.5 to 5.5, or fairly acid) thereby making it less susceptib bacterial infection.

Indications And Clinical Uses: Relieves vaginal dryness, itching and painful intercourse for up to 3 days with a sing application.

MANUFACTURERS' WARNINGS IN CLINICAL STATES: Keep out of the reach of children. Replens is not a contraceptive. Does not contain spermicide or hormones.

DOSAGE AND ADMINISTRATION: Use as needed. One application every 2 to 3 days is recommended.

INDICATIONS: Use as needed. One single application approximately once every 2 to 3 days is recommended.

INGREDIENTS: Purified Water, Glycerin, Mineral Oil, Polycarbophil, Carbomer 934P, Hydrogenated Palm Oil Glyc Sorbic Acid

WARNINGS: If an applicator is unwrapped or the wrapper is torn, do not use and return entire contents to place of purchase.

Replens is not a contraceptive. Keep out of the reach of children.

Store at room temperature (59-86F)

Availability: Usually ships in 2-3 business days.

Replens Vaginal Moisturizer 8 ct Prefilled Applicator Carton UPC: 0-21406-025-08-4 Regular price: $12.19 price: **$10.79** Minimum Order: 4 Order